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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,962	09/19/2007	Guy Michael Patrick	2713.0130000/BJD/GER	6858

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	**PAPER NUMBER**
1654	
MAIL DATE	**DELIVERY MODE**
04/27/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,962	PATRICK ET AL.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20, 23-24, 26, 28-31, 34-37, 40, 43-54* is/are pending in the application.

4a) Of the above claim(s) *30,31,34-37 and 43-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20, 23, 24, 26, 28, 29, and 52-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/17/2008 and 10/30/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-20, 23, 24, 26, 28, 29, and 52-54 in the reply filed on February 9, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election of the species Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$ in the reply filed on February 9, 2010 is also acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the claims

2. Claims 1-20, 23-24, 26, 28-31, 34-37, 40, 43-54 are currently pending. Claims 30-31, 34-37, 43-51 are withdrawn as not drawn to the elected group/species. Claims 1-20, 23, 24, 26, 28, 29, and 52-54 are presented for examination on the merits. Upon searching Examiner found other species encompassed by the instant claims which are herein examined for the sake of compact prosecution.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-7, 10-12, 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Claeson et al. (US 5,856,306) as evidenced by Elgendy et al. (The Design of Synthetic Inhibitors of Thrombin, 1993)

Claeson et al. teach a prodrug of boronic acids [Cbz-(R)-Phe-Pro-Mpg-BOPin, Pin = pinacolic ester] (cols. 4 and 13) which is a thrombin inhibitor and the compound has oral activity, rapid onset of activity and low toxicity as taught by Claeson et al. Further, Claeson et al. disclose oral and/or parenteral administration of the prodrugs. The prodrug is a solid (e.g., col. 13). The limitation "which have a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites" necessarily reads upon the structure of Cbz-(R)-Phe-Pro-Mpg-BOPin which anticipates the instantly claimed structural limitations of instantly claimed formulas I, III and IV.

Elgendy et al. is relied upon to evidence that the prodrugs containing pinacolic esters generate boronic acids (see Figure 1, Table 1) and that Cbz-(R)-Phe-Pro-Mpg-BOPin generates the corresponding boronic acid *in vivo* as shown in Figure 1 and therefore reads upon a prodrug of Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$. The selectivity and Ki are shown in Table 2. See, e.g., pages 173-176. With regards to the limitation "adapted for reconstitution of the formulation to form a liquid preparation" this reads upon, e.g., making dilutions or suspensions of the composition as described in the instant specification, which is taught by Claeson et al. and Elgendy et al.

Therefore the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-7, 10-12, 14-15, 20, 23, 26, 28 and 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable Claeson et al. (US 5,856,306) in view of Elgendy et al. (The Design of Synthetic Inhibitors of Thrombin, 1993) and Baschang et al. (US 4,959,394).

Elgendy et al. and Claeson et al. are relied upon as above.

Further, Claeson et al. disclose the thrombin inhibitor Cbz-(R)-Phe-Pro-Mpg-BOPin and its synthesis (e.g., cols. 4, 8, 13). Further, the reference teaches that the peptide boronic pinanediol ester may be converted to the free acid form by a method in which the pinanediol boronate is first reacted with one equivalent of methylithium and subsequently with HCl and methanol to give a borinate ester containing the group B(CH3)(OCH3). Treatment of this with I2/NaOMe in THF gives the dimethyl boronate ester, which hydrolyses readily in water to the free acid Cbz-(R)-Phe-Pro-Mpg-BOH2 (e.g., col. 6). Claeson et al. teach that the compounds have thrombin inhibition (anti-thrombogenic effect) and may be employed for indications when an anti-thrombogenic agent is indicated. Claeson et al. disclose oral and/or parenteral administration. In the case of larger mammals such as humans, the compounds may be administered alone or in combination with pharmaceutical carrier or diluent at a dose from 0.02 to 15 mg/Kg

of body weight and preferably 1-10 mg/Kg to obtain the anti-thrombogenic effect, and may be given a single or multiple doses, or as sustained release compositions. Although Claeson et al. do not teach expressly powders or specific packaging such as sachets and sealed containers, one of ordinary skill in the art at the time the invention was made would have been motivated to use available physical forms such as powders/sachets to deliver the compounds as taught by Baschang et al. which teach that formulations that can be dissolved to form liquid oral forms of administration, such as water-soluble powders and effervescent powders, preferably in single dose sachets, effervescent tables or reconstitutable dry syrups, are based on the reaction of a pharmaceutically acceptable organic acid with an alkali metal or alkaline earth metal carbonate compound, in which carbon dioxide is liberated and can be used in the delivery of pharmaceutical compounds which are organic acids (e.g. cols. 5-9). One of ordinary skill in the art at the time the invention was made would have been had a reasonable expectation of success since both the compounds of Claeson et al. and of Baschang et al. were known to be pharmaceutically orally acceptable and had acidic properties. With regards to the amount packaged, and the different solution pHs claimed, "[g]enerally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." (MPEP 2144.05).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

7. Claims 8-9, 13, 16-19 and 29 under 35 U.S.C. 103(a) as being unpatentable Claeson et al. (US 5,856,306) in view of Elgendy et al. (The Design of Synthetic Inhibitors of Thrombin, 1993), Baschang et al. (US 4,959,394) and Adams et al. (US 5,780,454).

Elgendy et al., Claeson et al. and Baschang et al. are relied upon as above.

Neither reference expressly teach multivalent salts of the boronic acid thrombin inhibitors.

Adams et al. teach boronic acid thrombin inhibitors for medicinal use, and pharmaceutically acceptable formulations comprising a multivalent metal ion. Water-soluble salts are preferable, including divalent ion salts such as alkaline earth metal salts such as magnesium, calcium, etc. (e.g., col. 9 and claims).

Further, neither reference appears to specifically name the compound Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-BOH2 with the stereoisomers in the Pro and Mpg as instantly claimed. With regards to the chiral centers, one of ordinary skill in the art would have been motivated to determine the chirality and also find any activity differences among stereoisomers of a given pharmaceutically active compound. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of

success since such determinations are routinely made in the laboratory by the artisan of ordinary skill in the art and because it was known that most compounds are normally synthesized as racemic mixtures containing several stereoisomers at once.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1-20, 23, 24, 26, 28, 29, and 52-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-92 of U.S. Patent No. 7,112,572 in view of Baschang et al. (US 4,959,394).

Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to an oral dosage form of a compound selected from boronic acids which have a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, and salts thereof, the dosage form comprising a solid phase formulation and include the instantly claimed species (e.g., Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$). With regards to the limitation "being adapted for reconstitution of the formulation to form a liquid preparation" the disclosure of US '572 was consulted as a dictionary and it teaches at col.33 that solid dosage forms for oral administration includes powders and granules and may contain a dissolution aid. Further, liquid dosage forms include pharmaceutically acceptable solutions (Col. 34). With regards to the limitation drawn to

an effervescent system/tablet in claim 24, it would have been obvious to make effervescent compositions for oral delivery. One of ordinary skill in the art at the time the invention was made would have been motivated to use any kind of oral dosage including effervescent tablets/granules since such kind of delivery was widely known and advantageously applicable to lyophilized drugs as taught, e.g., in Baschang et al. (US 4,959,394). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since Baschang et al. taught that formulations that can be dissolved to form liquid oral forms of administration, such as water-soluble powders and effervescent powders, preferably in single dose sachets, effervescent tables or reconstitutable dry syrups, are based on the reaction of a pharmaceutically acceptable organic acid with an alkali metal or alkaline earth metal carbonate compound, in which carbon dioxide is liberated and can be used in the delivery of pharmaceutical compounds which are organic acids (e.g. cols. 5-9) and which are also taught by US '572.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

10. Claims 1-20, 23, 24, 26, 28, 29, and 52-54 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-48 of U.S. Patent No. 7,371,729 (cited in the IDS dated 6/17/2008) in view of Baschang et al. (US 4,959,394). Although the conflicting claims are not identical, they are not patentably distinct from each other because both inventions are drawn to an oral dosage form of a compound selected from boronic acids which have a neutral thrombin

P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, and salts thereof, the dosage form comprising a solid phase formulation and include the instantly claimed species (e.g., Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$). With regards to the limitation "being adapted for reconstitution of the formulation to form a liquid preparation" column 75 US '729 teaches administering after reconstitution as an aqueous parenteral solution. Although oral administration is not taught by US '729 claims, one of ordinary skill in the art would have been motivated to try other ways of administration such as intranasal and/or oral in order to determine favorable ways of administration. With regards to the limitation drawn to an effervescent system/tablet in claim 24, it would have been obvious to make effervescent compositions for oral delivery. One of ordinary skill in the art at the time the invention was made would have been motivated to use any kind of oral dosage including effervescent tablets/granules since such kind of delivery was widely known and advantageously applicable to organic acids as taught, e.g., Baschang et al. (US 4,959,394). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since reasonable expectation of success since Baschang et al. taught that formulations that can be dissolved to form liquid oral forms of administration, such as water-soluble powders and effervescent powders, preferably in single dose sachets, effervescent tables or reconstitutable dry syrups, are based on the reaction of a pharmaceutically acceptable organic acid with an alkali metal or alkaline earth metal carbonate compound, in which carbon dioxide is liberated and can be used in the delivery of

pharmaceutical compounds which are organic acids (e.g. cols. 5-9) which are also taught by US '729.

Thus, the invention as a whole is prima facie obvious over the references, especially in the absence of evidence to the contrary.

11. Claims 1-20, 23, 24, 26, 28, 29, and 52-54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 10/592,265 in view of Baschang et al. (US 4,959,394). Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications teach compounds such as Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-B(OH) and administration to a patient. Although oral administration is not taught by US '265 claims, one of ordinary skill in the art would have been motivated to try other ways of administration such as intranasal and/or oral in order to determine favorable ways of administration. With regards to the limitation drawn to an effervescent system/tablet in claim 24, it would have been obvious to make effervescent compositions for oral delivery. One of ordinary skill in the art at the time the invention was made would have been motivated to use any kind of oral dosage including effervescent tablets/granules since such kind of delivery was widely known and advantageously applicable to organic acids as taught, e.g., Baschang et al. (US 4,959,394). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success since Baschang et al. taught that formulations that can be dissolved to form liquid oral forms of administration, such as water-soluble powders and effervescent powders, preferably in single dose sachets,

effervescent tables or reconstitutable dry syrups, are based on the reaction of a pharmaceutically acceptable organic acid with an alkali metal or alkaline earth metal carbonate compound, in which carbon dioxide is liberated and can be used in the delivery of pharmaceutical compounds which are organic acids (e.g. cols. 5-9) is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

12. No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

14. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Examiner, Art Unit 1654

MMCG 04/2010